Neuroendocrine carcinoma of the cervix: The value of postoperative radiation in early-stage disease[*]

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Abstract

Objective: The current treatment for early-stage neuroendocrine carcinoma of the cervix (NECC) mainly relies on operation and chemotherapy. We want to evaluate values of postoperative radiation in early-stage NECC.

Methods: Retrospective cohort study. Early-stage NECC patients from 2006 to 2022 in our hospital were included. Depending on whether received postoperative radiation, the patients were divided into Postoperative non-radiation group (Group A) and Postoperative radiation group (Group B). We use Kaplan-Meier method to analyze the progression-free survival (PFS), overall survival (OS), recurrence and OS rate.

Results: Sixty-six cases were included, 32 (48.5%) in Group A and 34 (51.5%) in Group B. After 35 (range 12-116) months follow-up, 26 (39.4%) had recurrence. Compared with Group A, Group B had lower pelvic recurrence rate (12.5% vs 2.9%, $p = 0.142$), higher distant recurrence rate (28.1% vs 44.1%, $p = 0.177$), and similar mortality rate (29.4% vs 31.3%, $p = 0.871$). Cervical stromal invasion ≥1/2 was more common in Group B (28.0% vs 63.0%, $p = 0.012$). Postoperative radiation in patients with cervical stromal invasion ≥1/2 showed an extended trend in PFS (33.9 months vs 47.9 months) and OS (40.7 months vs 70.0 months) but without statistical difference ($p = 0.963$, $p = 0.636$). Lymph-vascular space invasion (LVSI) is a high-risk factor for tumor recurrence (HR 9.13, $p = 0.005$), but radiation after surgery did not improve the PFS (51.5 months vs 48.8 months, $p = 0.942$) and OS (53.9 months vs 60.6 months, $p = 0.715$) in patients with LVSI.

Limitations: Retrospective study and relative small sample size.

Conclusions: Postoperative radiation seems to prolong PFS and OS in patients with cervical stromal invasion ≥1/2. LVSI was a high-risk factor for tumor recurrence, but radiation after surgery in patients with LVSI seems have no survival benefits.

Keywords: Neuroendocrine carcinoma; Cervical cancer; Radical hysterectomy; Postoperative radiation therapy; Overall survival.

1. Introduction and Literature review

Neuroendocrine carcinoma of the cervix (NECC) is an extremely rare and aggressive form of cervical cancer, accounting for about 1-2% of all cervical cancers [1,2]. The biology of NECC is different from squamous cell carcinoma or adenocarcinoma of the cervix. For example, lymph-vascular space invasion (LVSI) and regional lymph node metastases are more common at the time of NECC diagnosis. The overall survival rate of NECC is significantly worse than that of conventional cervical cancers [1].

Given the aggressive nature of NECC, the American Society of Gynecologic Oncology (SGO) and the Gynecologic Cancer Inter-Group (GCIG) both recommend radical hysterectomy plus lymphadenectomy for early-stage NECC with the etoposide/platinum-based adjuvant chemotherapy [3-5], but there is no consensus on which patients should receive postoperative radiation therapy. As more than half of the patients with NECC still relapse within 5 years despite radical hysterectomy and chemotherapy [6,7], some centers have routinely given radiation therapy after surgery regardless of pathologic factors while others utilize radiation only for patients with additional high-risk pathologic factors. Many studies shows that the addition of radiation therapy after surgery decreases pelvic tumor recurrences [7,8]. In a recent meta-analysis, Kim et al [9] reported that the routine radiation therapy after surgery in early-stage NECC could decrease pelvic tumor recurrences but do not decrease mortality. But for patients with high-risk pathological factors, postoperative radiation therapy still has its value. What is the actual reason for decreased pelvic recurrences unable to translate into a survival benefit? Is the pelvic radiation cannot prevent distant metastasis? Or because postoperative radiation therapy delayed postoperative chemotherapy? Either or patients who received supplementary

postoperative radiation therapy have more risk pathologic factor and theoretically worse prognosis? Due to lack of pathologic results of radical hysterectomy specimens, the meta-analysis did not define the subgroup of patients who would benefit from radiation therapy after surgery. In our hospital, whether to supplement postoperative radiation therapy for early-stage NECC patients is based on the judgment of Gynecologic Oncologist and the four-factor model of cervical adenocarcinoma. The four-factor model means adenocarcinoma, LVSI, tumor diameter greater than 3 cm, and deep cervical stromal invasion. If any two of the four factors are met, postoperative radiation therapy may has potentially benefit.

For women with early-stage NECC, there is no known associated factors that predicts the actual value of postoperative radiation therapy. For example, a model which was commonly used for describing the value of patients with squamous cell carcinoma or adenocarcinoma of the cervix to radiation therapy after surgery (i.e. "Sedlis Criteria") [10]. In this study, we retrospective analyzed the high-risk pathologic factors of early-stage NECC in our center and evaluated the value of postoperative radiation therapy in these patients.

2. Methodology (Design/Approach)

We reviewed the early-stage NECC patients at Peking Union Medical College Hospital (PUMCH) from April 2006 to April 2022. The inclusion criteria were: (1) received radical hysterectomy + pelvic lymphadenectomy ± para-aortic lymphadenectomy for cervical cancer, (2) pathologically confirmed NECC, and (3) based on the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system [11] staged I-IIA. The exclusion criteria were: (1) the primary treatment was pelvic radiation therapy

not radical hysterectomy, (2) lack of postoperative chemotherapy, and (3) follow-up information was unavailable.

This retrospective cohort study was approved to waive informed patient consent by the PUMCH ethics committee (approval number: I-22PJ723, date of approval: November 11, 2022). Data extracted from the hospital information system and pathology information system included age at diagnosis, initial symptoms, type of human papilloma virus (HPV), maximum tumor diameter, imageology examination, pelvic examination, primary treatment, chemotherapy, postoperative radiation therapy, time of tumor recurrence, site of tumor recurrence, last follow-up time, histological type, heterogeneity, LVSI, cervical stromal invasion, immunohistochemical (IHC) results, and pelvic lymph nodes status. The date we retrieved the patients' data from hospital information system and pathology information system is November 2022, and the last follow-up time in this study is June 2023.

All pathological examinations were performed by two independent pathologists. Cases with mixed squamous cell carcinoma or adenocarcinoma present in the NECC of the cervix (exceeding 5% of the tumor) were regarded as "Mixed" form, otherwise were regarded as "Pure" form. Primary treatment including radical hysterectomy, chemotherapy, with postoperative radiation therapy or not. In this study, patients without postoperative radiation therapy were classified as postoperative non-radiation group (Group A), patients with postoperative radiation therapy were classified as postoperative radiation group (Group B). The main outcome event is progression-free survival (PFS) and overall survival (OS). PFS was calculated based on the time interval from the start of

primary treatment to tumor recurrence, progression, or to the final follow-up. OS was calculated based on the time interval from the start of primary treatment to patient's death.

Data are presented as mean ±standard deviation (SD) or median (range) for continuous variables and frequencies (corresponding percentages) for categorical variables. Continuous variables between groups were compared using independent sample t tests. Categorical data were analyzed with χ^2 test or Fisher's exact test. The recurrence risk factors identified and accessed by COX regression. Cumulative PFS and OS rates were calculated using the Kaplan–Meier survival analysis, and the survival curves were compared by log-rank test. SPSS software (SPSS version 26.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. In this study, all the patients were in early stage, the deaths were not enough to calculate the median survival time (the corresponding survival time in patients with cumulative OS rate at 50%). Therefore, the survival outcome was expressed by 3-year OS rate, 5-year OS rate, and mean survival time. A p value < 0.05 was considered statistically significant.

3. Results

Among the 152 patients with high-grade NECC in our department from April 2006 to April 2022, early-stage accounted for 50.7% (77/152). We excluded 11 patients (4 patients had pelvic radiation as primary treatment, 2 patients had incomplete follow-up information, and 5 patients lack postoperative chemotherapy). Sixty-six patients (66/77, 85.7%) included in the statistical evaluation at last.

The characteristics of the 66 patients are presented in Table 1. Among them, 32 (48.5%) were in the postoperative non-radiation group (Group A), and 34 (51.5%) in the postoperative radiation group (Group B). The mean age was 42.9±11.2 years. Vaginal

bleeding (51/66, 77.3%) was the most common symptom. Regarding surgical treatment methods of radical hysterectomy, 53.0% (35/66, 53.0%) were by open abdominal and (31/66, 47.0%) were by minimally invasive.

In this study, all patients (n=66) received postoperative chemotherapy. Chemotherapy regimens included (1) Platinum plus Etoposide (46/66, 69.7%), (2) Platinum plus Paclitaxel (15/66, 22.7%), (3) Cisplatin plus Fluorouracil (3/66, 4.6%), (4) Cisplatin plus Ifosfamide (1/66, 1.5%), and (5) Cisplatin + Irinotecan (1/66, 1.5%). The most common regimen was Platinum plus Etoposide, followed by Platinum plus Paclitaxel. Pelvic external beam radiotherapy to a total dose of 45–50 Gy with (or without) vaginal brachytherapy was generally given for patients with postoperative pelvic radiation.

After 35 (range 12-116) months of follow-up, 26 patients (39.4%) had recurrence, there were 11 (34.4%) in the Group A and 15 (44.1%) in the Group B ($p = 0.418$). There was no statistical difference in median follow-up time between the two groups (38.5 months *vs* 29.5 months, $p = 0.460$). The median time from initial treatment to recurrence was 13.5 (4-41) months. There were 5 pelvic recurrences (7.6%), 24 distant recurrences (36.4%), and 3 both pelvic and distant recurrences (4.5%). Compared with the Group A, the Group B had a lower pelvic recurrence rate (12.5% *vs* 2.9%, $p = 0.142$) and a slightly higher distant metastasis rate (28.1% *vs* 44.1%, $p = 0.177$). Table 2 shows the initial recurrent sites. The most common site was the lung (18/26, 69.2%), followed by the liver (8/26, 30.8%) and the vaginal stump (4/26, 15.4%).

As shown in Table 3, LVSI, cervical stromal invasion ≥1/2, and number of pelvic lymph nodes excision ＜20 were evaluated as potential risk factors associated with postoperative recurrence. Multivariate analysis identified LVSI as an independent

predictor for postoperative recurrence (HR 9.13, 95%CI 1.93-43.17, $p = 0.005$). We identified no significant differences between other factors ($p > 0.05$).

We conducted a detailed evaluation of the pathologic factors in patients without preoperative chemotherapy (in order to exclude the impact of preoperative chemotherapy on postoperative pathology). As shown in Table 4, compared with Group A, the cervical stromal invasion ≥ 1/2 was more common in Group B (28.0% *vs* 63.0%, $p = 0.012$). In addition, the tumor diameter in Group B is larger than Group A (2.3cm *vs* 3.0cm, $p = 0.026$). The results indicate that the patients in Group B contained more high-risk pathologic factors than patients in Group A. We did not identify significant differences between other factors ($p > 0.05$).

Among the 66 patients, 20 patients (30.3%) died during the follow-up period. There were 10 (31.3%) in the Group A and 10 (29.4%) in the Group B ($p = 0.871$). The postoperative 3-year and 5-year OS rate was 77.8%, 59.9%, respectively. Compared with the Group B, the Group A had slightly higher 3-year and 5-year OS rates (81.9% *vs* 73.2%), (64.3% *vs* 55.6%) but without statistical difference ($p = 0.415$, $p = 0.512$). The cumulative PFS and OS rates in both groups are shown in Figure 1.

We compared the PFS and OS in patients with different pathologic factors and treatment methods. As shown in Table 5, in patients with cervical stromal invasion ≥1/2, postoperative radiation showed an improvement in PFS (33.9 months *vs* 47.9 months) and OS (40.7 months *vs* 70.0 months) but without statistical difference ($p = 0.963$, $p = 0.636$). Notably, although LVSI is a high-risk factor for tumor recurrence, the radiation therapy after surgery of the LVSI patients had no survival benefit. We found no improvement of the PFS (51.5 months *vs* 49.8 months, $p = 0.942$) and OS (53.9 months

vs 60.6 months, $p = 0.715$) in LVSI patients with postoperative radiation or not. We also compared the open abdominal radical hysterectomy and minimally invasive radical hysterectomy. The two groups had similar PFS (72.8 months *vs* 67.2 months, $p = 0.831$), OS (84.2 months *vs* 76.1 months, $p = 0.735$), the 3-year OS rate (76.8% *vs* 78.9%, $p = 0.850$), and the 5-year OS rate (65.8% *vs* 57.1%, $p = 0.711$).

4. Discussion

NECC is rare, but highly aggressive and with poor prognosis. It was first described by Reagan JW in 1952 [12]. In this study, we evaluated the value of postoperative radiation in early stage NECC patients with different pathological factors. According to the results, the primary site of recurrence in early-stage NECC was mainly outside the pelvis. Postoperative radiation can help to reduce pelvic recurrence but not appear to decrease overall recurrence or death. For early stage NECC patients with cervical stromal invasion ≥1/2, radiation therapy after surgery had a trend to improve PFS and OS but with no significant difference. Multivariate analysis identified LVSI as high-risk factor for postoperative tumor recurrence, but radiation after surgery in LVSI patients seemed have no survival benefit.

In the fifth edition of WHO Classification of Women's Reproduction Organ Tumors in 2020, neuroendocrine tumor were divided into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas [13]. The latter includes small cell and large cell subtypes, of which the small cell subtype is the most common pathological subtype. In our study, small cell subtype accounted for 78.8% in all early-stage NECC patients, which is similar to previous study (around 80.0%) [1].

The 5-year OS rate in this study was 59.9%, which is slightly higher than 31%-51% that reported in previous literature with early-stage NECC [14]. In a multicenter retrospective study conducted in Korea, LEE JM et al [15] reviewed a total of 68 patients with FIGO stage IA-IIA small cell NECC, the 5-year OS rate was 46.6%. In another retrospective study conducted in Japan, Ishikawa et al [7] enrolled 93 patients with NECC of FIGO stage I-II from database of 26 member hospitals, the 5-year OS rate was 54.9%. Chen et al [16] conducted a multicenter retrospective study in Taiwan that included 144 patients with early-stage NECC, the 5-year OS rate was 51%. The OS rates in the above studies were slightly lower compared to this study may be because the patients enrolled in the study were restaged by 2018 FIGO staging system, in which patients with lymph node metastases were excluded (staged IIIC in 2018 FIGO staging system). The rate of pelvic lymph node metastases in early-stage NECC is 22.5%-29% [16,17] and lymph node metastases is a high-risk factor for poor prognosis. Among women with early-stage cervical cancer, previous study showed that minimally invasive radical hysterectomy was associated with relatively poorer PFS and OS than open abdominal radical hysterectomy [18]. In our study, we did not find the survival benefit in open abdominal radical hysterectomy. The two groups had similar PFS and OS, 3-year and 5-year OS rate.

Given the rarity of NECC, there are limited data to guide treatment and no prospective trials to test and verify the optimal management. Treatment considerations generally extrapolated from retrospective study and the experience with small cell lung cancer [19]. Postoperative chemotherapy is recommended for all early-stage NECC patients due to highly tumor recurrence rate [3]. Cohen et al [20] shows that chemotherapy can reduce the recurrence rate by 38% compared with surgery only. Pei et al [21] also shows that patients

who did not receive chemotherapy after early-stage NECC had a 5.4-fold increased risk of recurrence. However, postoperative radiation therapy of early-stage NECC is still in controversial.

In 93 patients with stage I-II NECC who underwent radical hysterectomy, the pelvic recurrence rate was 16% *vs* 25% in patients with or without postoperative pelvic radiation [7]. Similarly, in a study of 110 patients with early-stage small cell NECC, the women who received postoperative radiation therapy had a lower pelvic recurrence rate than women who did not (13% *vs* 31%) [16]. However, routine postoperative radiation after surgery seems do not decrease mortality. Kim et al [9] reported that 12.5% pelvic recurrences in patients who received radiation therapy after surgery compared to 24.3% pelvic recurrences among patients who did not ($p = 0.09$), but the mortality rate was similar in both groups (34.8% vs 35.2%, $p = 0.66$). The actual reason why the decreased pelvic recurrences unable to translate into survival benefit remains unclear.

Like previous studies, we found a lower pelvic recurrence in NECC patients with postoperative radiation therapy. We further analyzed factors that may associated with PFS and OS. The patients who underwent postoperative radiation usually have additional high-risk pathologic factors (i.e., deep cervical stromal invasion). However, both groups had similar cumulative PFS and OS indicates that there may still be a role for postoperative radiation in subgroup of high-risk patients. Subgroup analyses showed postoperative radiation in patients with cervical stromal invasion ≥1/2 had a trend of prolonging PFS and OS (postoperative radiation increased PFS by 14.0 months and OS by 29.3 months) but without significant difference ($p = 0.963$, $p = 0.636$). Notably and interestingly, although LVSI is an independent predictor for postoperative recurrence, the

postoperative radiation in these patients seemed have no PFS (51.5 months *vs* 49.8 months, $p = 0.942$) and OS (53.9 months *vs* 60.6 months, $p = 0.715$) benefits. Analyzing the reasons, LVSI may be more related to tumor hematogenous metastasis and extra-pelvic recurrence, while cervical stromal invasion may be more related to pelvic reginal recurrence. Therefore, postoperative radiation for the latter seems have more potential survival benefit.

A multi-center study found that LVSI was associated with unfavorable prognosis in NECC patients. They concluded that NECC requires systemic chemotherapy as part of the initial treatment, along with surgery or radiation, even in patients with early-stage disease. However, they did not analyze whether radiation therapy has survival benefit for LVSI patients [22]. There are currently two hypotheses regarding the effect of pelvic radiation therapy on distant metastatic lesions. Firstly, some believed that postoperative pelvic radiation may promote distant recurrence in high-risk patients. Studies of animal models of lung cancer have shown that the rate of distant metastasis increased after local radiotherapy [23], associated reason maybe the local effect of radiation on blood vessels may promote tumor cell attachment, migration, and entry into the peripheral circulation. Secondly, other studies showed that radiation has a "remote effect", that is, local radiation may induce a systemic anti-tumor response outside the radiation field. However, it is difficult to infer which mechanism is more favorable.

The advantages of this study are as follows: (1) the single-center study ensures the consistency of surgical and pathological diagnosis, (2) only patients with early-stage NECC who underwent radical hysterectomy and postoperative chemotherapy were enrolled, which ensured the consistency of treatment strategies, and (3) subgroup analysis

of surgical pathologic results was performed. The limitations of this study are the retrospective nature and relative small sample size. However, due to the rarity of NECC (1-2% of all cervical cancers), it is difficult for a single center to include enough samples for prospective studies to elucidate the impact of treatment methods on survival outcomes. In future, a multicenter study should be considered to explore the value of postoperative radiation therapy in patients with cervical stromal invasion ≥1/2. Based on the result of ours, the calculated sample size is 262 high-risk patients per group, which means a sample size of 262 patients in each group provides a statistical power (1- β) of 80 % at α = 0.05 for the detection of 11.8 % difference (56.1% *vs* 67.9%) in proportion of 3-year OS rate (or any other condition) between the two groups.

5. Conclusion

We found the initial site of recurrence in early-stage NECC was mainly outside the pelvis. Postoperative radiation seems to prolong PFS and OS in patients with cervical stromal invasion ≥1/2. LVSI was a high-risk factor for tumor recurrence, but radiation after surgery in patients with LVSI seems have no survival benefits.

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DISCLOSURE OF INTEREST

All the authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the fundings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PEER REVIEW STATEMENT

Peer review model: Open peer review

Identity transparency: all identities visible

Reviewer interacts with: Editor

Review information published: review reports, submitted manuscript, reviewer identities, author/editor communication, editor identities.

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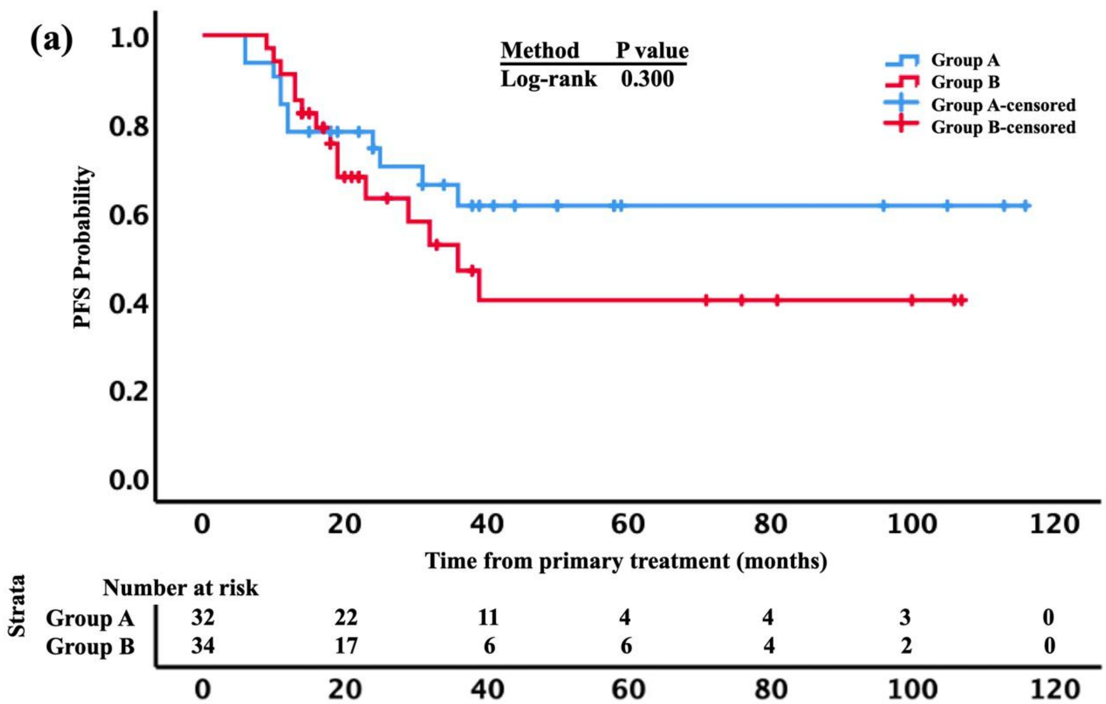
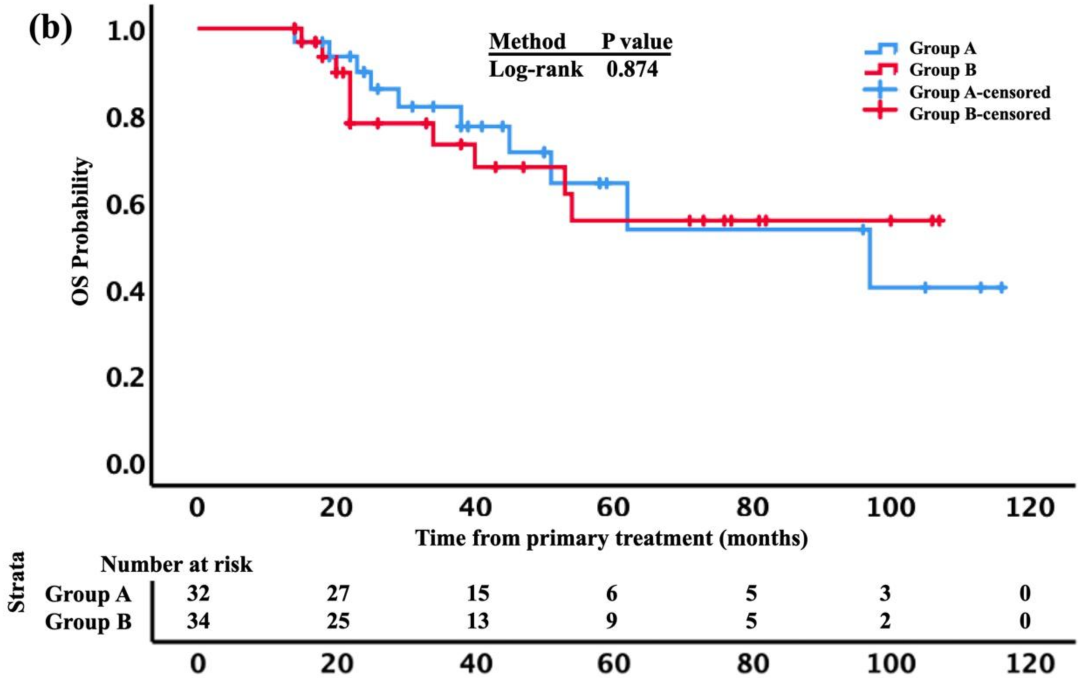
Figure Legends

Fig. 1. Estimates of (a) progression-free survival (PFS) and (b) overall survival (OS) of the postoperative non-radiation group (blue, Group A) and postoperative radiation group (red, Group B). X-axis: time from primary treatment (months). Y-axis: PFS/OS probability (1.0 represents 100%).

Figures




(b)
1.0
0.8
0.6
0.4
0.2
0.0
OS Probability
Method P value
Log-rank 0.874
Group A
Group B
Group A-censored
Group B-censored
0 20 40 60 80 100 120
Time from primary treatment (months)
Strata
Number at risk
Group A 32 27 15 6 5 3 0
Group B 34 25 13 9 5 2 0
0 20 40 60 80 100 120

Tables

Table 1[a] Clinical and demographic characteristics of the 66 patients

Baseline characteristics	Total n=66	Group A n=32	Group B n=34	*p* values
Age (years)	42.9±11.2	40.4±10.1	45.2±11.8	0.080
Body mass index (kg/m²)	23.3±2.8	23.0±3.0	23.7±2.5	0.399
Parity	1 (0-4)	1 (0-3)	1 (0-4)	0.714
Symptoms				0.339
Vaginal bleeding	51 (77.3%)	25 (78.1%)	26 (76.5%)	
Vaginal discharge	5 (7.6%)	1 (3.1%)	4 (11.8%)	
None	10 (15.2%)	6 (18.8%)	4 (11.8%)	
HPV infection[b]				0.610
Type 18	29 (76.3%)	16 (%)	13 (%)	
Other types	8 (%)	4 (%)	4 (%)	
Negative	1 (%)	0 (%)	1 (%)	
Maximum tumor diameters (cm)	3.0±1.4	2.8±1.4	3.3±1.4	0.146
Tumor polypoid appearance	15 (22.7%)	7 (21.9%)	8 (23.5%)	0.873
Tumor stage				0.512
Stage I				
IA1	0 (0%)	0 (%)	0 (%)	
IA2	2 (3.0%)	2 (6.3%)	0 (0.0%)	
IB1	16 (24.2%)	9 (28.1%)	7 (20.6%)	
IB2	32 (48.5%)	15 (46.9%)	17 (50.0%)	

IB3	7 (10.6%)	3 (9.4%)	4 (11.8%)	
Stage II				
IIA1	4 (6.1%)	2 (6.3%)	2 (5.9%)	
IIA2	5 (7.6%)	1 (3.1%)	4 (11.8%)	
Preoperative chemotherapy	14 (21.2%)	7 (21.9%)	7 (20.6%)	0.898
Surgical approach				0.611
Open abdominal	35 (53.0%)	18 (56.3%)	17 (50.0%)	
Minimally invasive	31 (47.0%)	14 (43.8%)	17 (50.0%)	

[a] The data are presented as the mean ± standard deviation, median (range), or n (%).

[b] HPV, Human Papilloma Virus, data missing in 28 cases (12 cases in Group A, 16 cases in Group B).

Table 2[a] The initial recurrent sites of the 66 patients

Initial recurrent sites	Total n=66	Group A n=32	Group B n=34	*p* values
Tumor recurrences	26 (39.4%)	11 (34.4%)	15 (44.1%)	0.418
Pelvic recurrences	5 (7.6%)	4 (12.5%)	1 (2.9%)	0.142
Vaginal stump	4	3	1	
Pelvic lymph node	1	1	0	
Pelvic wall	1	1	0	
Distant recurrences	24 (36.4%)	9 (28.1%)	15 (44.1%)	0.177
Lung	18	8	10	
Mediastinal lymph nodes	3	1	2	
Diaphragm	1	0	1	
Chest wall	1	0	1	

Abdominal wall	1	1	0
Liver	8	4	4
Pancreas	2	2	0
Adrenal gland	1	1	0
Kidney	1	0	1
Spleen	1	1	0
Supraclavicular lymph nodes	1	0	1
Bone metastasis	4	1	3

[a] Some patients had multiple recurrence sites. Three patients had both pelvic and distant recurrences.

8 **Table 3** Univariate and multivariate analyses of postoperative recurrence in 66 cases

Variables	Postoperative recurrence			
	Univariate analysis		Multivariate analysis	
	p values	HR (95%CI)	*p* values	HR (95%CI)
Age (years)				
＜45 *vs* ≥45	0.326	1.47 (0.68-3.19)		
Body mass index (kg/m^2)				
≤25.0 *vs* ＞25.0	0.752	0.82 (0.24-2.83)		
Histological type				
Non-small cell *vs* Small cell	0.860	0.91 (0.31-2.64)		
Tumor heterogeneity				
(Pure *vs* Mixed)	0.946	1.03 (0.47-2.27)		
Maximum tumor diameter				
＜4cm *vs* ≥4cm	0.182	1.71 (0.78-3.78)		
Lymph-vascular space invasion				
(No *vs* Yes)	**0.001**	**11.78 (2.78-49.98)**	**0.005**	**9.13 (1.93-43.17)**
Cervical stromal invasion ≥1/2				
(No *vs* Yes)	**0.011**	**3.08 (1.29-7.36)**	0.613	1.27 (0.51-3.16)
Tumor polypoid appearance				
(No *vs* Yes)	0.262	0.54 (0.19-1.58)		
Preoperative chemotherapy				
(No *vs* Yes)	0.184	1.76 (0.76-4.06)		
Chemotherapy course ≥4				
(No *vs* Yes)	0.696	1.27 (0.38-4.26)		

Surgical methods				
(Open abdominal *vs* Minimally invasive)	0.832	1.09 (0.50-2.36)		
Number of pelvic lymph nodes excision				
(＜20 *vs* ≥20)	**0.009**	**0.36 (0.17-0.77)**	0.417	0.72 (0.33-1.59)
Postoperative radiation therapy				
(No *vs* Yes)	0.306	1.51 (0.69-3.29)		

[a]Potential risk factors with p ≤ 0.1 in univariate regression were analyzed in a multivariate regression; HRs with 95% CIs are presented.

Bold values indicate potential risk factors related to postoperative recurrence according to the univariate and multivariate regression analyses.

Table 4 Surgical pathological analysis of both groups (excluding 14 patients with preoperative chemotherapy)

Variables	Total n=52	Group A n=25	Group B n=27	*p* values
Histological type				0.324
Small cell	41 (78.8%)	19 (76.0%)	22 (81.5%)	
Large cell	9 (17.3%)	4 (16.0%)	5 (18.5%)	
Small & large cell	2 (3.8%)	2 (8.0%)	0 (0)	
Histological heterogeneity				0.609
Pure type	31 (59.6%)	14 (56.0%)	17 (63.0%)	
Mixed type	21 (40.4%)	11 (44.0%)	10 (37.0%)	
Maximum tumor diameter (cm)	**2.7±1.1**	**2.3±1.1**	**3.0±1.0**	**0.026**
Stratification of maximum tumor diameter				0.031
≤2cm	17 (32.7%)	12 (48.0%)	5 (18.5%)	
> 2, ≤4cm	32 (61.5%)	13 (52.0%)	19 (70.4%)	
> 4cm	3 (5.8%)	0 (0)	3 (11.1%)	

Tumor polypoid appearance	14 (26.9%)	7 (28.0%)	7 (25.9%)	0.866
Number of pelvic lymph nodes ≥20	41 (78.8%)	21 (84.0%)	20 (74.1%)	0.381
Cervical stromal invasion ≥ 1/2	**24 (46.2%)**	**7 (28.0%)**	**17 (63.0%)**	**0.012**
Lymph-vascular space invasion	29 (55.8%)	11 (44.0%)	18 (66.7%)	0.100
Vaginal invasion	4 (7.7%)	2 (8.0%)	2 (7.4%)	0.936
Course of chemotherapy ≥ 4	43 (82.7%)	23 (92.0%)	20 (74.1%)	0.088
Immunohistochemical staining				
Chromogranin A positive (n = 47)	37 (78.7%)	19 (82.6%)	18 (75.0%)	0.717
Synaptophysin positive (n = 47)	42 (89.4%)	21 (91.3%)	21 (87.5%)	0.771
CD56 positive (n = 37)	28 (75.7%)	13 (72.2%)	15 (78.9%)	0.758

Table 5 Comparison of survival outcomes in patients with different pathologic factors and treatment methods

Variables	Number	PFS (months)	*p value*	OS (months)	*p value*	3-year OS (%)	*p value*	5-year OS (%)	*p value*
Pathologic factors									
Cervical stromal invasion ≥1/2	35		0.963		0.636		0.753		0.636
Postoperative non-radiation group	13	33.9 (21.3-46.6)		40.7 (30.3-51.1)		56.1		44.9	
Postoperative radiation group	22	47.9 (28.2-67.8)		70.0 (51.1-88.8)		67.9		53.5	
Lymph-vascular space invasion	38		0.942		0.715		0.611		0.983
Postoperative non-radiation group	16	51.5 (31.6-71.3)		53.9 (32.9-74.9)		68.2		36.4	
Postoperative radiation group	22	49.8 (35.9-63.5)		60.6 (42.7-78.5)		59.6		44.2	
Maximum tumor diameter ≥ 4cm	19		0.835		0.501		0.657		0.618
Postoperative non-radiation group	9	68.9 (34.5-103.3)		84.7 (56.6-112.8)		74.1		49.4	

Postoperative radiation group	10	48.9 (21.8-75.9)		59.2 (33.2-85.3)		66.7		35.6	
Tumor stage ≥ Ⅰb3 (2018 FIGO)	16		0.281		0.593		0.759		0.848
Postoperative non-radiation group	6	35.3 (25.1-45.5)		40.3 (33.9-46.6)		75.0		37.5	
Postoperative radiation group	10	46.2 (19.9-72.5)		68.9 (42.8-95.1)		76.2		47.6	
Treatment methods									
Surgical approach	66		0.831		0.735		0.850		0.711
Open abdominal	35	72.8 (53.3-92.3)		84.2 (65.8-102.7)		76.8		65.8	
Minimally invasive	31	67.2 (49.9-84.6)		76.1 (60.6-91.6)		78.9		57.1	
Course of chemotherapy	66		0.693		0.467		0.484		0.585
< 4	10	74.8 (50.9-98.7)		81.4 (59.4-103.4)		90.0		67.5	
≥4	56	69.1 (54.9-83.3)		77.6 (64.2-90.9)		76.0		59.2	
Course of chemotherapy ≥4	56		0.309		0.705		0.313		0.407
Postoperative non-radiation group	30	76.9 (58.6-95.1)		77.9 (60.3-95.7)		81.4		63.9	
Postoperative radiation group	26	53.1 (33.3-72.8)		70.7 (51.8-89.6)		67.8		52.3	

FIGO, International Federation of Gynecology and Obstetrics. PFS, progression-free survival. OS, overall survival